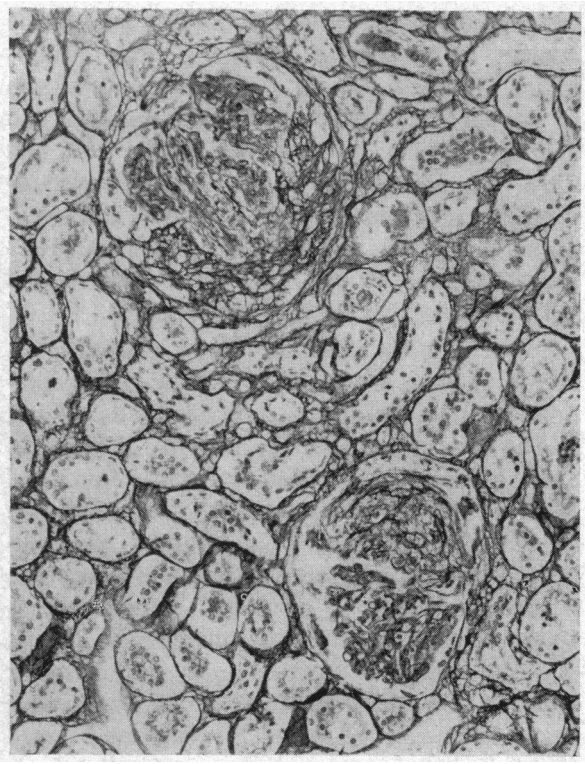

Figure 8.—Section of kidney demonstrating pronounced proliferation of reticulum fibers at the site of a glomerular crescent (Silver impregnation. ×150).

systems. The course of illness was very short—seven days. Autopsy findings were consistent with the early stages of the natural history of the disease.

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Hemophilus Aphrophilus Endocarditis

Successfully Treated With Ampicillin and Streptomycin

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THE FIRST KNOWN infection caused by *Hemophilus aphrophilus* was bacterial endocarditis in a 28-year-old woman who lived 165 days after admission to the hospital in 1938.[13] The name *Hemophilus aphrophilus* was chosen by Khairat[13] because of the hemophilic character of the organism, its dependence on hemin (*x* factor) and its enhanced growth in carbon dioxide. (Aphros from the Greek, meaning foam, refers to the carbon dioxide bubbles forming on wine vats during fermentation.) The organism does not require diphosphopyridine nucleotide (*v* factor) for growth. There have been fewer than 10 reported cases of bacterial endocarditis caused by this organism.* In only one case, that reported by Quinn and coworkers,[19] was the patient treated with ampicillin.

From the Department of Internal Medicine, White Memorial Medical Center, Los Angeles.

Submitted 11 January 1966.

*Reference Nos. 12, 19, 21, 23, 26.

In the present case, the organism that grew on 12 blood cultures was identified as *Hemophilus aphrophilus* by the Department of Public Health Bacteriological Laboratories, State of California, and the U.S. Public Health Service, Communicable Disease Center, Atlanta, Georgia.

Report of a Case

A 24-year-old Mexican man, a printer, was admitted to the White Memorial Hospital on 6 April 1965, with complaint of fever of 10 days' duration. He had not had recent dental work. He had had a heart murmur since age 16 and a history of probable rheumatic fever at age eight. Five years before admission, cardiac catheterization at Stanford University Medical Center established a diagnosis of mitral insufficiency. The patient had never had symptoms or signs of congestive heart failure. He had never received penicillin prophylaxis or digitalis.

On physical examination, the patient's oral temperature was 38.4°C (101.2°F). The pulse was regular at 108 per minute, the respiratory rate was 18 per minute and the blood pressure was 130/76 mm of mercury. The patient appeared well. The optic fundi were normal, and there were no dental caries, petechiae, splinter hemorrhages or clubbing. There was a moderate left ventricular heave with the point of maximum impulse palpable 2 cm lateral to the mid-clavicular line in the left 6th intercostal space. No thrill was palpated. A grade 4 (of 6) harsh, blowing, pansystolic murmur was heard at the apex and radiated toward the axilla. A faint diastolic rumble was heard at the apex with the patient in the left lateral decubitus position. The first heart sound at the apex was loud and the pulmonary second sound was accentuated. The lungs were clear. The liver was not palpable. The tip of the spleen was palpated beneath the left costal margin. All arterial pulses were normal.

The urine was clear and it did not contain protein, red cells or casts. The hemoglobin was 13.5 gm per 100 ml and the hematocrit 42 per cent. Leukocytes numbered 9,500 per cu mm with 37 per cent lymphocytes, 2 per cent monocytes, 1 per cent basophils and 55 per cent polynuclear and 5 per cent band neutrophils. The sedimentation rate (Westergren) was 68 mm in one hour. The two-hour post prandial blood sugar 128 mg, serum bilirubin 0.6 mg and the blood urea nitrogen 7 mg per 100 ml. Antistreptolysin 0 titer was 166 Todd units. A serological test for syphilis was nonreactive. Serum sodium, potassium and carbon dioxide content were normal. Serum protein electrophoresis showed 4.0 gm of albumin and 4.3 gm of globulins per 100 ml, with elevated alpha 2 and gamma globulin fractions measuring 870 and 2,075 mg per 100 ml respectively. An electrocardiogram showed sinus tachycardia and occasional premature ventricular contractions. Teleroentgenograms of the chest demonstrated mild left ventricular and left atrial enlargement.

In view of the persistent fever, splenomegaly, known valvular heart disease, elevated sedimentation rate and abnormal content of serum proteins, it was decided to treat the patient for bacterial endocarditis in spite of the fact that after four days' incubation there was no growth of organisms on six blood cultures drawn on admission. Six additional blood cultures were drawn and therapy was begun, consisting of a continuous intravenous infusion daily of 15,000,000 units of penicillin G, plus streptomycin, 1 gm daily, by intramuscular injection. On the sixth hospital day, colonies of small Gram-positive bacilli first appeared on all six of the blood cultures drawn on the day of admission, which had been incubated with 5 per cent carbon dioxide. The organism appeared to be of the *Hemophilus* species but not *H. influenza.*

By the eighth hospital day, there had been no clinical response to therapy. Since ampillicin has good activity in vitro against *H. influenza* and has been used successfully in the treatment of other *Hemophilus* infections,[10,16,20,22] use of this antibiotic was started on the eighth hospital day and penicillin G was discontinued. Ampicillin (Polycillin-N®), 2 gm diluted in 50 ml of water, was given intravenously by rapid infusion every four hours, the 24-hour dose being 12 gm. In addition, the streptomycin was increased to 2 gm intramuscularly each day. The patient did not have undesirable side effects. Ampicillin was continued at 12 gm daily for 29 days and streptomycin was given concurrently in a dose of 2 gm daily for 24 days. On the sixth day of ampicillin therapy, the temperature became normal. No splinter hemorrhages, petechiae or Osler's nodes were noted during the patient's 38 days in hospital. The character of the cardiac murmur did not change. The spleen, which was palpable 4 cm below the left costal margin on the 14th hospital day, was not palpable at the time of discharge. The sedimentation rate (Westergren) was 68 mm in one hour on admission, rose to a maximum of 109 mm on the eighth

hospital day, dropped to 26 mm at the time of discharge, and one month after discharge was 5 mm in one hour. Serial blood cell counts, urinalysis, and blood urea nitrogen determinations remained within normal limits. A repeat series of blood cultures drawn on the 25th hospital day and incubated with penicillinase were sterile. An electrocardiogram and x-ray films of the chest showed no change from those taken at the time of admission. Serum protein electrophoresis determination was approaching normal a week before the patient was discharged, with albumin 4.6 gm and globulin 3.7 gm per 100 ml with a minimal elevation of gamma globulin. The patient remained well during six months of observation after leaving the hospital.

Bacteriological data is presented in Table 1. The colonies were small—0.15 to 0.4 mm in diameter—smooth, glistening and translucent, and they produced an olive green discoloration on the blood agar plate. The presence of 5 per cent carbon dioxide was necessary for maximum growth and in its absence both aerobic and anaerobic cultures grew very poorly. Microscopically, the organisms were Gram-negative, nonmotile short rods and coccobacilli. Optimum growth occurred at 37°C with no growth at 25°C and 42°C.

This organism conforms to Khairat's original description[13] and with the extensive characterization of *H. aphrophilus* by King and Tatum.[14] With minor variations, the organism was similar to that described by Russell,[21] who discussed the differential isolation and identification of the Gram-negative pleomorphic bacilli. Table 2 lists antibiotic sensitivity values as well as the patient's serum antibacterial titer. Serum drawn four hours after an ampicillin dose was bactericidal at a dilution of 1:256 against the organism isolated from cultures drawn on the fourth hospital day.

TABLE 1.—*Culture Characteristics and Fermentation Profile of Hemophilus Aphrophilus Species Isolated*

Blood agar with 5 per cent CO_2	Maximum growth
MacConkey media	No growth
SS Media	No growth
Leoffler's Media	
Pigment	Negative
Proteolysis	Negative
Catalase	Negative
Oxidase	Weakly positive
Gelatin	Negative
Litmus milk	Negative
Citrate	Negative
Indol	Negative
Urea	Negative
Nitrate	Negative
Fermentation Base	Beef Extract and Serum
Xylose	Negative
Mannitol	Negative
Salicin	Negative
Glucose	Acid and gas bubbles 2nd day
Of media + glucose—	
open	Acid
closed	Acid
Lactose	Acid and gas bubbles 2nd day
Maltose	Acid and gas bubbles 2nd day
Sucrose	Acid and gas bubbles 2nd day

TABLE 2.—*Antibiotic Sensitivity Values of Hemophilus Aphrophilus Species Isolated*

1. Disc Sensitivity (10 microgram discs):		
Penicillin G		sensitive
Ampicillin		sensitive
Streptomycin		sensitive
2. Tube dilution sensitivity:	Bacteriostatic level:	Bactericidal level:
Penicillin G.	0.20 micrograms per cc.	0.80 micrograms per cc.
Ampicillin	Less than 0.10 micrograms per cc.	0.20 micrograms per cc.
Patient's Serum*	1:256 dilution	1:256 dilution

*Serum drawn four hours after an ampicillin dose and incubated with organisms isolated from cultures drawn on the fourth hospital day.

Comment

The U.S. Public Health Service Communicable Disease Center in Atlanta, Georgia, has identified 94 strains* of *H. aphrophilus* from human infections.[15] Positive cultures have been obtained from the following sources: blood, 43; spinal fluid, 5; brain abscess, 18; sinusitis, 6; finger abscess, 1; superficial skin infections, 11; cervix, 1; chest sinus, 1; thoracentesis fluid, 2; bronchus, 1; periappendiceal abscess, 1; unknown, 1. Although the precise number of positive cultures from patients with endocarditis is unknown because case histories are no longer being requested with cultures, the majority of the 43 positive blood cultures were from patients with endocarditis.

It is of interest that in two cases of brain abscess caused by *H. aphrophilus* reported by Fager[3] and by Isom and coworkers,[9] positive cultures were obtained from pet dogs who often licked the patients' necks. The patient in the case herein reported did not have a dog, but often had contact with a poodle belonging to a friend. The poodle often licked the patient on the face and extremities. The dog's saliva was cultured and found negative for *H. aphrophilus*. In addition, the patient's wife and child had throat cultures negative for *H. aphrophilus*.

In six of the nine reported cases of *H. aphro-*

*As of October 1965.

TABLE 3.—*Summary of Clinical Findings in Nine Reported Cases of H. Aphrophilus Endocarditis*

Patient Reported by Sex	*Age*	*Heart Disease Background*	*Predisposing Factors*	*Treatment*	*Result*
Keith and Lyon[12]..M	66	Rheumatic	Dental extraction	Penicillin, 20 million units for 32 days; streptomycin, 1 gm for 14 days; tetracycline, 2 gm for 3 days; and colistin, 1 gm for 17 days	Cured
Khairat,[13] 1940 ....F	28	Rheumatic	Not stated	Sulfonamides	Died
Quinn, et al.[19].....M	50	Unknown	None known	Penicillin G, 20 million units for ? days	Died*
Russell,[21] 1965.....M	59	Unknown	Superficial skin infection, left foot	Keflin,® 3 gm for 2 days and 2 gm for 14 days, then 1.5 gm for 2 days, relapse, then treated with Keflin, streptomycin and Kanamycin, unknown amounts for 18 additional days	Cured
Toshach and Bain,[23] 1958 .....M	47	?Rheumatic (calcific aortic stenosis)	Heart block, aortic sinus aneurysm	Penicillin, chloramphenicol, chlortetracycline and oxytetracycline	Died
Witorsch and Gordon[26]—					
Case 1, 1955.....F	28	Rheumatic	Upper respiratory	Penicillin, 6 million units for 14 days; probenecid, 2 gm for 14 days, and streptomycin, 1 gm for 14 days	Cured
Case 2, 1963.....M	35	Rheumatic	Dental cleaning	Penicillin, 50 million units for 21 days; streptomycin, 2 gm for 14 days and 1 gm for 7 days	Cured
Case 3, 1963.....M	25	Uncertain	Dermatitis; steroids	Penicillin, 30 million units for 28 days; streptomycin, 1 gm for 30 days; and chloramphenicol, 3 gm for 17 days	Cured
Present case .....M	24	Rheumatic	None known	Penicillin G, 15 million units for 4 days, ampicillin, 12 gm for 29 days, streptomycin, 1 gm for 4 days and 2 gm for 24 days	Cured

*Bacteriologically sterile at autopsy

philus endocarditis cure was obtained with a variety of antibiotics (see Table 3). Khairat's original case occurred before the antibiotic era. Five of the nine patients had had rheumatic heart disease. It seems that the type of bacterial endocarditis caused by this organism is similar to the more common *Streptococcus viridans* variety and tends to attack previously damaged heart valves.

On the basis of in vitro studies of the organism cultured in the present case, one would expect ampicillin to be superior to penicillin G for the treatment of *H. aphrophilus* endocarditis. The report by Quinn and coworkers[19] of a case of *H. aphrophilus* endocarditis treated with ampicillin describes in vitro sensitivities to ampicillin and penicillin G similar to those found in the present case. In their case, the minimum bactericidal concentration for penicillin G was 6.25 micrograms per milliliter compared with 0.049 micrograms per milliliter for ampicillin.

The value of a bactericidal antibiotic in treating bacterial endocarditis has been frequently stressed,[4,6,8,25] and experience in treating infection with other *Hemophilus* species[10,22] would indicate an even greater necessity for a bactericidal drug because of the high relapse rate associated with *Hemophilus* infections. It was for these reasons that ampicillin in a large dosage was given in the present case. In retrospect, a smaller dose might have been successful, and streptomycin may have been unnecessary.

In a study of review articles* on bacterial endocarditis published during the last 15 years, covering a total of 1,403 cases, it was noted that there were 10 cases caused by *Hemophilus* organisms excluding the *H. aphrophilus* strain. In addition, Jones[11] found 23 cases of *Hemophilus* endocarditis in his extensive survey of 212 cases of nonstreptococcal bacterial endocarditis reported in the world literature between 1936 and 1948. His report included Khairat's case caused by *H. aphrophilus*. These reports,† with a total of 32 cases of *Hemophilus* endocarditis excluding the aphrophilus type, suggest that *Hemophilus* organisms rarely cause endocarditis; the total number makes up less than 1 per cent of all bacterial endocarditis. However, when organisms of the *Hemophilus* group are isolated, the aphrophilus species should be suspected in view of its increasing frequency of isolation.

*Reference Nos. 1, 2, 5, 6, 7, 17, 18, 24, 25.
†Reference Nos. 1, 2, 5, 6, 7, 11, 17, 18, 24, 25.

Summary

In a patient who probably had had rheumatic heart disease, bacterial endocarditis caused by *H. aphrophilus* developed years later. The infection was successfully treated with parenteral ampicillin and streptomycin. Bacteriological data, and in vitro antibiotic sensitivity studies are presented. The eight previously reported cases of bacterial endocarditis caused by this organism are reviewed with treatments compared, including one case treated with ampicillin. The role of this organism in other human infections with the proportion of positive cultures from various sources as confirmed by the Communicable Disease Center, Atlanta, Georgia, is presented. Available data suggest ampicillin is effective in treating infections caused by this organism.

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GENERIC AND TRADE NAMES FOR DRUGS

Ampicillin—*Polycillin-N.*
Cephalothin—*Keflin.*

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Hodgkin's Disease Terminating in Chronic Myeloid Leukemia

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HODGKIN'S DISEASE is an ever popular subject in the medical literature because of its protean manifestations and the diversity of its course. It was first described in 1832 by Thomas Hodgkin as "a disorder affecting the absorbent glands and spleen," and its cause has yet to be determined.[18] Although it is classed with the malignant lymphomas the histologic character of Hodgkin's disease bears

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